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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	**PAPER NUMBER**
1634	

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11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/695,065	Applicant(s) BRASCH ET AL.	
	Examiner Frank Lu	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-20,27 and 30-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-20,27 and 30-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on January 17, 2002 has been entered as Paper No:10. The claims pending in this application are claims 14-20, 27, and 30-43. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 16-20, 27, 31, and 33-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Note that claims 17-20, 27, 31, 33, and 33-43 are dependent on claim 16.

Claim 16 is rejected as vague and indefinite over the phrase "inserting one or more integration sequences each comprising at least one recombination site into at least one nucleic acid molecule" because "each" in this phrase suggests more than one integration sequences. Please clarify.

Claim Rejections - 35 U.S.C. § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
>
> (f) he did not himself invent the subject matter sought to be patented.

5. Claims 14-20, 27, 32, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Stemmer et al., (US Patent No. 5,605,793, published by February 25, 1997).

Stemmer teaches method for *in vitro* recombination which can be used in many different genes encoded proteins. One aspect of this invention provided a method for introducing one or more mutations into a template double-stranded polynucleotide, wherein the template double-stranded polynucleotide had been cleaved into random fragments of a desired size, by adding to the resultant population of double-stranded fragments one or more single or double-stranded oligonucleotides, wherein said oligonucleotides comprised an area of identity and an area of heterology to the template polynucleotide; denaturing the resultant mixture of double-stranded random fragments and oligonucleotides into single-stranded fragments, incubating the resultant population of single-stranded fragments with a polymerase under conditions which resulted in the annealing of said single-stranded fragments at regions of identity between the single-stranded fragments and formation of a mutagenized double-stranded

polynucleotide; and repeating the above steps as desired (column 3, second paragraph). Either synthetic or natural single-stranded or double stranded nucleic acid fragments could be added to the random double-stranded nucleic acid fragments in order to increase the heterogeneity of the mixture of nucleic acid fragments (see column 7). In example 1, the substrate for the reassembly reaction was the dsDNA PCR product of the wild-type LacZ alpha gene from pUC18 (see claims 15 and 27) (FIG. 2). About 5 μg of the DNA substrate was digested with DNaseI. The 10-70 bp fragments were purified and were used for DNA reassembly by PCR in the absence of primer. The product of DNA reassembly could be further amplified by PCR with primers. Finally, the PCR product was digested with restriction enzymes BamHI and Eco0109 and the reassembled fragments were ligated into a suitable vector (see columns 11 and 12). Note that: (1) any 10-70 bp fragment that were inside PCR product could be considered as an integration sequence as recited in claims 14 and 16; (2) dsDNA PCR product of the wild-type LacZ alpha gene could be considered as a nucleic acid molecule flanked by recombination sites as described in claim 14 or comprising at least a first and a second recombination sites as described in claim 16 wherein BamHI and Eco0109 cloning sites could be considered as first and a second recombination sites and were separated by at least a portion of said nucleic acid molecule as recited in claims 16, 18, 32, and 33; (3) the vector containing dsDNA PCR product of the wild-type LacZ alpha gene was a circular molecule as recited in claim 17; and (4) although Stemmer did not show that 10-70 bp fragments (see above) comprised selectable markers as described in claim 20, in the absence of convincing evidence to the contrary, these limitations is considered to be inherent to the reference taught by Stemmer since these fragments could bind T4 polynucleotide kinase (a

product that modify a substrate, see the specification, page 27) and labeled P^{32} in the 5' end of this fragments.

Therefore, Stemmer teaches all limitations recited by claims 14-20, 27, 32, and 33.

Response to Arguments

In page 8, second paragraph bridging to page 9, first paragraph of applicant's remarks, applicant argued that: "[S]temmer patent does not expressly or inherently disclose, in an enabling fashion, methods for transferring nucleic acid molecules into vectors via recombinational cloning," since "[S]temmer does *not* disclose the use of " recombinational cloning" as that term is defined in the present specification.".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, The examiner noted that there was a definition for "recombinational cloning" in the specification (see page 26) which cited US Patent No. 5, 888,732 as a example. Since "recombinational cloning" in column 8 of US Patent No. 5, 888,732 was defined as a recombinational cloning method "whereby segments of DNA molecules are exchanged, inserted, replaced, substitutes or modified, in vitro or vivo.", the examiner considered that Stemmer's patent taught all limitations recited by claims 14-20 and 27 because Stemmer disclosed *in vitro* recombination by introducing one or more mutations (insertion and modification) into a template double-stranded polynucleotide (see above).

6. Claims 16-20 , 27, 32, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Atlung *et al.,* (Gene 107, 11-7, October 1991).

Atlung *et al.*, teach a versatile method for integration of modified genes and gene fusions into the bacteriophage lambda attachment site (attB) of the Escherichia coli chromosome. As shown in Figure 2, the method use two components to perform the recombination: (1) a DNA integration cassette, flanked by multiple restriction enzyme sites, which contained the lambda attP site and, as a selectable marker, the Tn5 aphA gene conferring kanamycin resistance (Km^R); and (2) a plasmid with the lambda int gene transcribed from the tet promoter. A fragment carrying the gene in question was ligated to the integration cassette, resulting in a circular piece of DNA as recited in claim 17 unable to replicate. The ligation product was then transformed into a strain that contains the int-carrying plasmid. Selection for Km^R resulted in colonies with the cassette integrated into the attB site of the E. coli chromosome (see abstract in page 11 and page 14). Note that two ligation sites between the DNA integration cassette and the plasmid could be considered as first and second recombination sites as described in claim 16.

Therefore, Atlung *et al.*, teach all limitations recited by claims 16-20 , 27, 32, and 33.

Response to Arguments

In page 10, first paragraph bridging to page 11, second paragraph of applicant remarks, applicant argued that "[A]tlung does not expressly or inherently disclose methods of recombinational cloning involving at least two recombination sites on a single nucleic acid molecule," since (1) "ligation sites (or, more accurately, restriction sites) do not quality as 'recombination sites," and (2) "[A]tlung fails to disclose the use of nucleic acid molecules comprising at least two (i.e., at least a first and a second) recombination sites on a single nucleic

acid molecule, which are then recombined (although not necessarily with each other) via recombinational cloning.".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, ligation sites (restriction sites) could be considered as "recombination sites" since "recombination site" was defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see specification, page 23, last paragraph) and ligase could be considered as a recombination protein (see specification, page 23 for definition of "recombination proteins"). Second, claim 16 does not require the use of nucleic acid molecules comprising at least two recombination sites for recombination. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

7. Claims 14-20, 27, and 30-43 are rejected under 35 U.S.C. 102(a) or 102 (e)) as being anticipated by Hartley *et al.,* (US Patent No. 5,888,732, filed on June 7, 1996 and published on March 30, 1999).

Hartley *et al.,* teach a method of making chimeric DNA which comprised: (1) combining in vitro or in vivo (I) an insert donor DNA molecule, comprising a desired DNA segment flanked by a first recombination site and a second recombination site, wherein the first and second recombination sites do not recombine with each other; (ii) a vector donor DNA molecule

containing a third recombination site and a fourth recombination site, wherein the third and fourth recombination sites do not recombine with each other; and

(iii) one or more site specific recombination proteins capable of recombining the first and third recombinational sites and/or the second and fourth recombinational sites; and (2) producing at least one cointegrate DNA molecule, at least one desired product DNA molecule which comprised said desired DNA segment, and a Byproduct DNA molecule (for example, see columns 4-7 and 19-22, and Figures 1, 2A, 3A, and 4A). This method could be used different kind of DNA fragments such as genomic DNA or cDNA recited in claims 15 and 27 (see column 11). Note that: (1) nucleic acid sequence between attp and loxp sites in plasmid pEZC726 of Figure 2A could be considered as a nucleic acid molecules flanked by recombination sites as recited in claim 14; (2) two lox P sites in plasmid pEZC7cointegr could be considered as a first and a second recombination sites of a produced nucleic acid molecule recited in claims 16, 18, 30-35, and 40-43; (3) Intprod or Intbypro in Figure 2A could be considered as a circular molecule generated from recombination of the first and second recombination sites as recited in claim 17; (4) nucleic acid sequence having kam marker could be considered as the integration sequence as recited in claim 14, 19, and 20; and (5) alternatively, one loxP and attL sites in plasmid pEZC7cointegr could be considered as a first and a second recombinant sites as recited in claims 36-39.

Therefore, Hartley *et al.,* teach all limitations recited in claims 14-20, 27, and 30-43.

8. Claims 14-20, 27, and 30-43 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

The above patent was filed on June 7, 1996 and published on March 30, 1999 and taught all limitations recited in claims 14, 16-20, and 30-43 (see above). However, the assignee in above patent (Life Technologies, Inc.,) was not be considered as coinventors for this instant application (assignee was Invitrogen Incorporation). Please give explanation.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 14-20, 27, and 30-43 are rejected under the judicially created doctrine of double patenting over claims of U. S. Patent No. 5,888,732 since the claims 1-3 and 29-37, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as

follows: Independent claim 29 in U. S. Patent No. 5,888,732 and independent claims 14 and 16 in this instant application are directed to the methods which are directed to the same scope and common subject matter. Note that claims 14 and 16 in this instant application are much broader than claim 29 in U. S. Patent No. 5,888,732.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

(1) The prior art that can be used for rejections under 35 U.S.C. 102(e) or 102(f) and double patenting:

Hartley et al., (U.S. Patent Nos. 6,171,861 B1, 6,270,969, and 6,277,608)

(2) The prior art that can be used for rejections under 35 U.S.C. 102(e) or 102(f):

Hartley et al., (U.S. Patent No. 6,143,557)

11. Applicant was suggested to look their pending US Patent applications related to recombinational cloning for possible double patenting issue.

12. No claim is allowed.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
April 4, 2002

ETHAN C. WHISENANT
PRIMARY EXAMINER